

## **REMARKS**

### **Amendments to the Claims**

Claims 5-6, 12-38 and 40 have been canceled. Claims 43-50 have been added. The newly added claims do not add or constitute new matter, and are completely supported by the application as originally filed. Support may be found throughout the specification and in the originally filed claims. Specifically, support for the transgenic mice and methods of producing the same, recited in claims 43-50, may be found, for example, at page 55, line 11 through page 62, line 13, of the specification.

The amendments to the claims are made without prejudice to the pending or now-canceled claims or to any subject matter pursued in related applications. Moreover, the amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation or continuation-in-part application.

Upon entry of the foregoing amendments, claims 43-50 are pending in the instant application.

### **Sequence Compliance (Replacement Drawings)**

The Examiner has asserted that the instant application fails to comply with the requirements of 37 C.F.R. §§ 1.821 through 1.825. In particular, the Examiner has stated that the sequence disclosed in Figure 2A is unidentified.

Replacement Figure 2A, attached herewith, has been submitted in order to fully comply with the requirements of 37 C.F.R. §§ 1.821 through 1.825. The replacement figure merely adds a sequence identifier to the sequence disclosed in Figure 2A, which was inadvertently omitted. No new matter has been added by this amendment. The amendment is supported by the originally filed specification and figures. Specifically, support for the amendment may be found, for example, at page 12, lines 6-12 (the Brief Description of the Drawings) and in originally filed Figures 1A and 2A. Moreover, no new sequences have been added, as the sequence set forth in Figure 2A is identical to the sequence set forth in Figure 1A and SEQ ID NO:1. Thus, the sequence listing as filed May 22, 2002 contains all sequences disclosed in the instant application.

Applicant believes that this application fully complies with the requirements of 37 C.F.R. §§ 1.821 through 1.825.

**Rejections*****Rejections under 35 U.S.C. § 112, first paragraph***

Claims 5-6, 12-38 and 40 were rejected under 35 U.S.C. § 112, first paragraph, because, according to the Examiner, the specification does not enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with the claims. The Applicant respectfully traverses this rejection. However, in view of the cancellation of claims 5-6, 12-38 and 40, the Examiner's rejection under 35 U.S.C. § 112, first paragraph, is no longer relevant.

Specifically, according to the Examiner, while the specification has taught the generation of a transgenic mouse comprising a homozygous disruption of the sequence set forth in SEQ ID NO:1 having the following phenotypes: dwarfism, hunched posture, small eyes and ears, small thymus gland, a malformed femur, small skeletal muscle, decreased fat in the subcutis, small or not visible seminal vesicles, low body weight, short body length, low organ weight, low organ weight to body weight ratio, small thyroid gland with small follicles, abnormalities of the pituitary gland consisting of adenohypophysis, large and vacuolated cells, reduced chromophils, pars distalis, chromophobe hypertrophy, dysplasia of the epiphyses of the femur, tibia stifle joint, reduced patchy ossification of bones, reduced cellularity of bone marrow, hypoplasia with absence of corticomedullary distinction of the thymus gland, immature kidneys with small golmeruli, lymphocytic infiltrates in the kidneys, immature testes, hypospermatogenesis, in terstitial Leydig cell hyperplasia, oligospermia, lymphocytic infiltrates in the lungs, diffuse retinal fibrosis and elevated blood urea nitrogen, and methods of making the same and using the same to screen for agents that ameliorate a phenotype, the specification has not taught the generation of the other transgenic non-human animals encompassed by the claims.

As one aspect of the rejection, the Examiner asserts that although the specification has taught a method of producing the transgenic mouse, which requires the use of genetically manipulated embryonic stem cells, it has not taught how to create the transgenic mouse by a method that does not require embryonic stem cells. Applicant has overcome this aspect of the rejection by reciting the introduction of the targeting construct into a mouse embryonic stem cell, which is enabled by the specification.

The Examiner has further asserted that the breadth of the claims directed to transgenic non-human animals or the use of non ES cells to produce a transgenic mouse, are not enabled

due to the state of the art of ES cell technology, which is generally limited to the mouse system. As the pending claims now recite a transgenic mouse and a method of making the same using mouse embryonic stem cells, Applicant has overcome this aspect of the rejection.

Another aspect of the rejection is related to the phenotypes of the transgenic animals, and the state of the art with regard to the unpredictability associated with the phenotype of a transgenic/knockout mouse. Specifically, the Examiner states that certain of the claims either do not recite any phenotype, or recite phenotypes that are “overly broad and are not supported by the instant specification” (see Office Action dated September 26, 2003, page 8). The Examiner also asserts that the claims are not enabled by the specification because they allegedly encompass homozygous or heterozygous disruption of the TSH-R gene. Applicant contends that the pending claims, which now recite a homozygous transgenic mouse exhibiting a phenotype of reduced growth and development, are fully described in and enabled by the specification. Applicant submits that the specification describes the extensive characteristics of reduced or retarded growth and development exhibited by these transgenic mice in such a way as to enable one skilled in the art to make and use the transgenic mouse as claimed. Therefore, Applicant has overcome this aspect of the rejection, and submits that the transgenic mice and methods recited in claims 43-50 are fully enabled by the specification.

Applicant respectfully disagrees with the Examiner’s conclusions and traverses the rejection. However, the Applicant has canceled claims 5-6, 12-38 and 40 in order to expedite prosecution of the instant application. Further, new claims 43-50 have been submitted, which are believed to overcome the issues raised in the rejection under 35 U.S.C. § 112, first paragraph.

In light of the amendments to the claims and remarks set forth above, Applicant requests withdrawal of the rejection under 35 U.S.C. § 112, first paragraph. Applicant submits that pending claims 43-50 fully meet the requirements and are patentable under 35 U.S.C. § 112, first paragraph.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-666.

Respectfully submitted,

Date: \_\_\_\_\_

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I hereby certify that this correspondence and its listed enclosures is being deposited with the United States Postal Service as First Class Mail, postage paid, in an envelope addressed to: Commissioner for Patents, Mail Stop Non-Fee Amendment on **January 26, 2004**

Name: **Don Mixon**

Signed: \_\_\_\_\_

Don Mixon

Date: \_\_\_\_\_

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